Curr Neurol Neurosci Rep (2014) 14:471
DOI 10.1007/s11910-014-0471-7

CRITICAL CARE (SA MAYER, SECTION EDITOR)

Emergency Reversal of Anticoagulation: Novel Agents

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Published online: 27 June 2014

Abstract Historically, oral anticoagulation involved the administration of vitamin K antagonists, such as warfarin. However, because of the need for frequent monitoring and the desire for safer anticoagulants, several novel oral anticoagulants have been developed. These newer agents include the factor Xa inhibitors (eg, rivaroxaban, apixaban, edoxaban), along with the direct thrombin inhibitors (eg, dabigatran). This manuscript provides a brief overview of their uses and mechanisms of action, along with a review of currently available evidence for reversal strategies when life-threatening bleeding occurs.

Keywords Anticoagulants · Factor Xa inhibitors · Direct thrombin inhibitors · Coagulopathy

Introduction

During routine physiological conditions, the body maintains a constant balance between thrombus formation and destruction [1]. The interplay between the vascular endothelium, platelets, and the coagulation cascade promote thrombus formation, whereas the fibrinolytic system functions to degrade any existing thrombus. Alterations in this balance can result in either inappropriate thrombus formation or hemorrhage [1].

The coagulation cascade was traditionally perceived as 2 pathways working independently; an extrinsic pathway involving tissue factor (TF) and factor VIIa (FVIIa), and an intrinsic pathway (contact activation). More recently, the cell-based model of coagulation is more commonly described in which components of both pathways are intimately involved in producing thrombin, an enzyme critical in the coagulation cascade [1–3]. Tissue factor typically resides on fibroblasts, smooth muscle cells, and pericytes [4–6]. When factor VII binds to tissue factor, factor VII becomes activated (VIIa), which ultimately results in the activation of factors IX and X.

The contact activation pathway commences with the activation of factor XII [2]. This activation ultimately triggers a sequence of reactions, culminating in the conversion of X to Xa, the first step in the common pathway. The common pathway concludes with the conversion of fibrinogen to fibrin. While there are numerous steps involved in platelet aggregation and adhesion, fibrin produced from the coagulation cascade ultimately increases stability of the aggregated platelets through its effects on the glycoprotein IIb/IIIIa complex [7].

Historically, the only oral anticoagulant available was warfarin, which inhibits the conversion of vitamin K 2,3 epoxide to vitamin K quinone, as well as the conversion of vitamin K quinone to vitamin K quinol, the active form of vitamin K [8, 9]. Such inhibition prevents *gamma* carboxylation of vitamin K dependent clotting factors, namely factors II, VII, IX, and X, along with protein C and protein S. As a result, patients are simply missing effective forms of these factors, which leads to an increase in the prothrombin time (PT) and international normalized ratio (INR). In an attempt to develop a drug that does not require routine monitoring of the INR, and ideally leads to fewer bleeding complications, numerous different alternatives have been developed in recent years (Table 1). These novel anticoagulants target distinct areas on the coagulation cascade (Fig. 1). This manuscript discusses the novel oral anticoagulants, with regards to mechanism of action, associated laboratory abnormalities, and potentially available reversal strategies. Of note, while reversal strategies for

This article is part of the Topical Collection on *Critical Care*

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Table 1 Overview of novel oral agents

Agent	Target factor	Laboratory test	Possible reversal strategy
Warfarin	Factor II, VII, IX, X, protein C, protein S	PT/INR	Vitamin K, FFP, PCC
Dabigatran	Factor II	TT or ECT preferred; aPTT for screening. HEMOCLOT	None clearly established; FEIBA or activated PCC may work
Apixiban, Rivaroxaban	Factor X	PT or Factor Xa level; neither is ideal	PCC

aPTT activated partial thromboplastin time, *ECT* ecarin clotting time, *INR* international normalized ratio, *PT* prothrombin time, *TT* thrombin time.

warfarin can be focused on simply replenishing the missing coagulation factors, the new agents are active inhibitors. Patients taking these agents are not deficient in coagulation factors, making the question of how to "reverse" novel agents more complex. It is also less clear which laboratory test is best for marking whether a patient has been reversed [10].

Novel Oral Anticoagulants

Direct Thrombin Inhibitors

Mechanism of Action

The direct thrombin inhibitors (DTIs) are a class of drugs that are available for both oral and intravenous use. Unlike heparins, which inhibit thrombin indirectly via their action on antithrombin, the DTIs inhibit thrombin directly. Furthermore, unlike heparins, which require a cofactor to produce their desired anticoagulation, the DTIs do not require such a cofactor, and can inhibit thrombin independently [11•, 12]. This direct inhibition results in a more predictable pharmacokinetic and pharmacodynamics profile [11•]. The DTIs can be used for prophylaxis and treatment of venous thromboembolism, heparin-induced thrombocytopenia, acute coronary syndromes, and prophylaxis of thrombus formation in nonvalvular atrial fibrillation [13]. However, many of these indications are for parenterally administered drugs. Dabigatran, the only orally available DTI, is approved to prevent thrombus formation in nonvalvular atrial fibrillation as well as treatment of venothromboembolism in patients who have been treated with parenteral anticoagulation for 5–10 days previously [14].

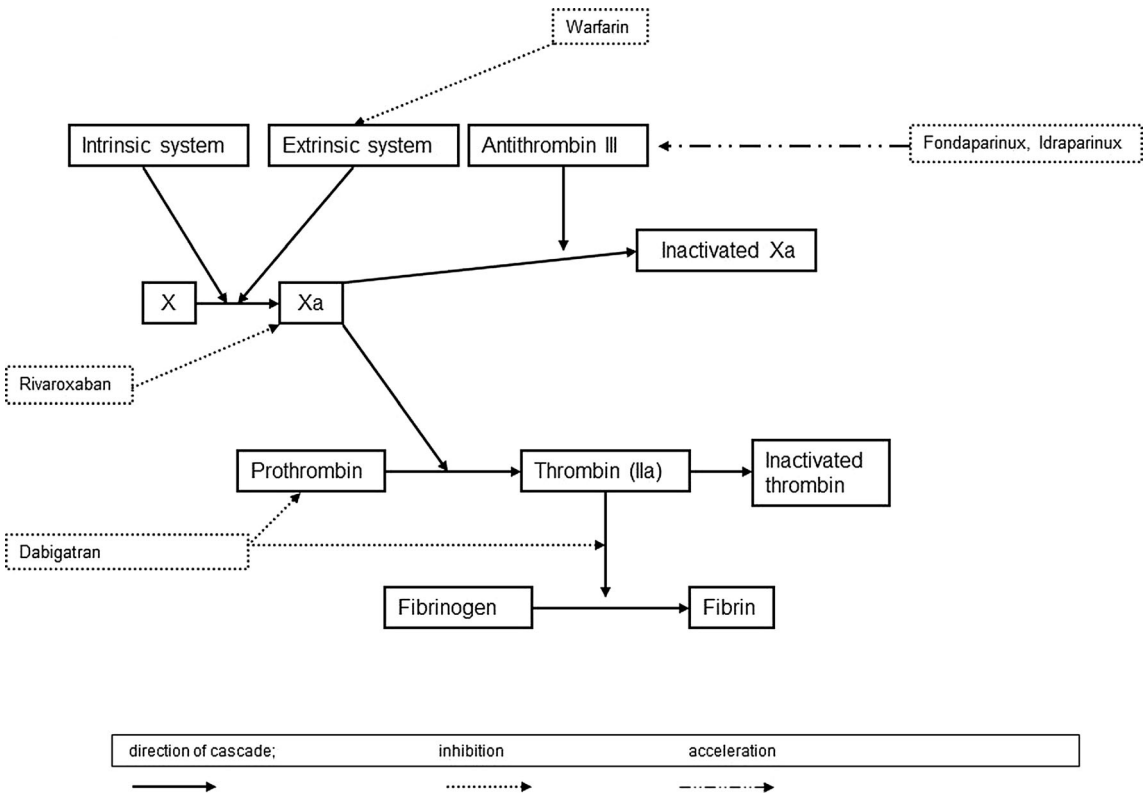

Fig. 1 This figure demonstrates the coagulation cascade and highlights were various novel anticoagulants work

The DTIs can be classified as bivalent, univalent, or allosteric, based on their binding site. Inhibition of thrombin can occur if the DTI binds to 1 exosite 1, exosite 2, or the active site. Exosite 1 serves to facilitate the substrate to achieve the correct orientation for binding to the active site, while exosite 2 is the binding domain for heparin [15]. Dabigatran binds to the active site of thrombin alone, and is considered a univalent DTI [15].

Following consumption, the ester of dabigatran etexilate mesylate is hydrolyzed, forming the active drug, dabigatran. The maximal concentration of dabigatran is achieved approximately 1 hour postconsumption. While dabigatran is neither a substrate, inducer, nor inhibitor of the P450 system, dabigatran etexilate is a P-glycoprotein substrate [14]. Consequently, inhibitors of P-glycoprotein would be expected to increase the concentration of dabigatran etexilate.

The primary toxicity in patients therapeutically consuming dabigatran is bleeding. The rate of bleeding appears to be dose-dependent [16, 17]. In addition, major bleeding is more common in those 75 years of age or older, compared with younger individuals [16].

Laboratory Monitoring

In concept, anticoagulation with DTIs can be monitored with a thrombin time (TT) or an ecarin clotting time (ECT) [18•]. However, neither of these tests is routinely available. The activated partial thromboplastin time (aPTT) can be used to screen for the presence of a DTI; a normal aPTT excludes significant anticoagulation [18•]. However, the aPTT reaches a plateau with direct thrombin inhibitors. Consequently, the degree of elevation in the aPTT does not correlate well with the degree of anticoagulation; it can only serve as a marker that there is some anticoagulation from a DTI present [19].

There is 1 DTI assay that has been published–the Hemoclot [20, 21]. This test is effectively a diluted thrombin time assay that can measure dabigatran activity. Finally, thromboelastography (TEG) has been used, both in vitro and in human subjects, to detect a range of coagulation disturbances, but this test is not yet routinely available and interpretable in clinical practice [22, 23].

Potential Reversal Strategies

There is no clearly established reversal strategy developed for dabigatran [18•, 19–24]. Some authors have examined various coagulation products, either with the goal of providing excess FII, or activating the coagulation system distally.

Basic Science Models

Recombinant factor VIIa (rFVIIa) can directly activate thrombin on the surface of platelets, suggesting a potential role in reversal [25]. In 1 in vitro study, rVIIa improved a range of thromboelastography (TEG) parameters in blood containing dabigatran [26].

Animal data has demonstrated the potential for a 4-complex prothrombin complex concentrate to provide partial reversal of dabigatran in a hemorrhage model [27, 28]. A direct antibody against dabigatran has been demonstrated to be helpful in a rodent model [29], but is not currently available in humans.

For ICH in particular, 1 mouse model of ICH suggested that both PCC and FFP could, to varying degrees, prevent DTI-induced hematoma expansion, whereas rFVIIa did not [29]. It is unclear whether the mouse coagulation system is different than in humans, or whether rFVIIa cannot effectively restore coagulation when FII is inhibited.

Human Studies

Thus far, studies in humans are aimed mostly at reversing laboratory abnormalities rather than clinical hemostasis. One group found that DTI-induced changes in PTT in healthy, nonbleeding volunteers could not be reversed with a nonactivated PCC (Cofact) [30]. However, another group compared a nonactivated 4-factor PCC (Kanokad), an activated PCC (FEIBA), and rFVIIa in samples from healthy volunteers that had been taking dabigatran. They examined whether DTI-induced laboratory abnormalities measured by TEG could be reversed in vitro [31]. They found that all 3 agents had some effect on altered coagulation parameters, although rFVIIa and FEIBA were more effective than nonactivated 4-F PCC. This suggests that there may be an advantage to providing activated rather than nonactivated factors. Unfortunately it is not yet clear which coagulation parameter is most relevant for this purpose, nor whether normalizing it would lead to hemostasis [32].

Current Guidelines

The American College of Cardiology Foundation and the American Heart Association recommend packed red blood cells and fresh frozen plasma (FFP), or surgical interventions to control bleeding [33•]. However, while the recommendation for packed red blood cell transfusion may support the patient who is bleeding, it is unlikely that FFP would be beneficial, as FFP contains factor II, but not IIa, and the presence of the DTI will prevent conversion of II to IIa [18•]. Suggestions from the Thrombosis and Hemostasis Society of North America suggest that activated charcoal may prevent absorption (if the last dose was recent enough), and that PCC may be the best of the currently available options [34••]. In addition, the German Society of Neurology recommends PCC for this purpose [35••].

Is There Enough Data for a Standard of Care?

No. At the moment, there is no clear data that any currently available agent effectively reverses DTI-induced coagulopathy. Two surveys of current practice, among hematologists and neurologists, suggest that PCC, FFP, and rFVIIa are all in use [36••, 37••]. For patients with impaired renal function, hemodialysis has been successfully utilized to reverse the anticoagulation effects of dabigatran, suggesting this as one treatment option [18•]. Otherwise, it appears reasonable to provide best medical management, avoiding the potential thromboembolic risks of procoagulant agents in the absence of a clear benefit. If the goal, however, is to provide a procoagulant agent of some kind, and the question is which of the currently available choices is most reasonable, it may be that FEIBA or a 4 F PCC would be the most effective option.

Factor Xa Inhibitors

Mechanism of Action

The factor Xa inhibitors are available for both oral and parenteral use. These drugs inhibit factor Xa, the first step in the common pathway on the anticoagulation cascade, and result in a dose-dependent inhibition of factor Xa [38]. Factor Xa inhibitors can be considered either direct inhibitors (eg, apixaban or rivaroxaban) or indirect inhibitors (eg, fondaparinux). Unlike the indirect factor Xa inhibitors, which bind to antithrombin III and subsequently produce a conformational change in it, the direct inhibitors can bind to the active site on factor Xa, resulting in inhibition independent of antithrombin III [39, 40]. Currently, there are 2 orally available factor Xa inhibitors in use in the US; rivaroxaban and apixaban. Edoxaban is available in other countries, but is not currently available in the US. Drugs in this class are approved for prevention of stroke prophylaxis in atrial fibrillation and for prophylaxis against deep vein thrombi and pulmonary embolism in patients undergoing hip or knee replacement [41].

Apixaban is an orally available factor Xa inhibitor, which inhibits both free and clot bound factor Xa, as well as prothrombinase activity. Following oral consumption, the maximal concentration is achieved 1–4 hours postconsumption [41, 42]. While apixaban neither induces nor inhibits any of the P450 isoenzymes, it is primarily metabolized via CYP3A4 [41, 42]. In addition, it is a substrate of P-glycoprotein [43]. Drugs which inhibit the metabolism of CYP3A4 or inhibit P-glycoprotein would be expected to increase the concentration of apixaban [41, 44].

Rivaroxaban is another orally available inhibitor of factor X, which also inhibits free factor Xa and prothrombinase activity. The maximal concentration of rivaroxaban occurs 2–4 hours after oral consumption [44]. It undergoes oxidative degradation by CYP3A4, CYP3A5, and CYP2J2 along with hydrolysis [44]. Drugs that inhibit the metabolism of these isoenzymes would be expected to increase the concentrations of rivaroxaban.

Laboratory Monitoring

The Factor Xa inhibitors may prolong the PT, but the degree of PT elevation does not directly correlate with that produced by the vitamin K antagonists [42]. Furthermore, the conversion of the PT to the INR with these drugs increases variably [10, 42]. It should be noted, however, that the elevation in PT is more pronounced in supratherapeutic concentrations of the factor Xa inhibitor [10]. Anti-factor Xa assays can be performed, but the test needs to be calibrated specifically for these drugs, rather than using the calibration scale designed for low molecular weight heparins [45]. In addition, the different anti-Xa assays demonstrated different ranges for each inhibitor [46].

Potential Reversal Strategies

As with DTIs, there is no clearly established reversal strategy developed for these agents. Some authors have examined various coagulation products, either with the goal of providing excess FX, or activating the coagulation system distally.

Basic Science Models

One rabbit model tested the ability of rVIIa and PCC for reducing apixaban-induced prolonged bleeding time and correcting various laboratory measures of hemostasis [47]. They found that PCC and rFVIIa shortened PT and improved some coagulation measures, and rFVIIa reduced bleeding time in vitro. However, neither agent improved clinical hemostasis. Similar findings were noted for rivaroxaban in the same model [48]. A model of rat, rather than rabbit, hemostasis suggested that both rFVIIa and PCC can reverse edoxaban-induced PT prolongation [49].

Of note, a mouse model of rivaroxaban-associated intracerebral hemorrhage noted that FFP, PCC, and rFVIIa all prevented hematoma expansion [29], it is unclear whether there are differences between rabbit and mouse coagulation systems, or whether ICH expansion represents a different measure of hemostasis than ear bleeding.

Human Studies

One group examined the ability of different agents to reverse rivaroxaban-induced coagulation abnormalities in healthy volunteers [30]. They found that a PCC (Cofact) reversed the PT prolongation and normalized the endogenous thrombin potential. Another group examined TEG-related changes in

human volunteers on rivaroxaban, and found that while non-activated PCC and rFVIIa corrected some of these abnormalities, FEIBA (activated PCC) corrected all abnormalities [31]. Finally, 1 group performed in vitro studies on human volunteer samples, and found that PCC corrected some but not all rivaroxaban-induced abnormal coagulation parameters [32].

Current Guidelines

The Thrombosis and Hemostasis Society of North America suggests that activated charcoal may prevent absorption (if the last dose was recent enough), and that 4 factor PCC may be the best of the currently available options [34••]. Unlike dabigatran, in which hemodialysis may be beneficial, the Thrombosis and Hemostasis Society of North America do not recommend hemodialysis for factor Xa inhibitors [34••]. In addition, the German Society of Neurology recommends PCC for this purpose [35••].

Is There Enough Data for a Standard Of Care?

No. At the moment, there is no clear data that any currently available agent effectively reverses Factor Xa-induced coagulopathy, either in vitro or in humans. As with the DTIs, it appears that current practitioners use any of PCC, FFP, and rFVIIa [36••, 37••]. Otherwise, it appears reasonable to provide best medical management, avoiding the potential thromboembolic risks of procoagulant agents in the absence of a clear benefit. If the goal is to provide a procoagulant agent of some kind, and the question is which of the currently available choices is most reasonable, it may be that FEIBA or a 4 F-PCC would be the most effective option.

Conclusions

The successful development of alternatives to warfarin has been a tremendous boon to clinicians and patients, providing new ways of preventing thromboembolism. However, it is not yet clear how best to reverse the novel anticoagulants, or even whether any currently available product can do so. National guidelines suggest that to the extent any agent might be effective, prothrombin complex concentrates may be the best of the available options.

Compliance with Ethics Guidelines

Conflict of Interest Michael Levine declares that he has no conflict of interest. Joshua N. Goldstein has received consultancy fees from CSL Behring.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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